IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Katarzyna JURECZEK
Title:	SUSTAINED RELEASE TABLET CONTAINING INDAPAMIDE
Appl. No.:	10/518,386
International Filing Date:	7/24/2002
371(c) Date:	5/3/2005
Examiner:	MICAH PAUL YOUNG
Art Unit:	1618
Confirmation Number	6605

DECLARATION OF KATARZYNA JURECZEK UNDER 37 C.F.R. § 1.132

Dear Examiner Young:

I, KATARZYNA JURECZEK, state and declare that:

1. I am the inventor of the invention recited in claims 1-6 of the patent application identified above and I am an employee of the assignee. I have reviewed the Office Action dated 6/27/2008 pertaining to the above-identified patent application and the three references cited by the Office (Damien *et al.*, Clin. Pharmacokinet. (1999) 37 Suppl. 1; Tobin et al., U.S. Patent No. 6,077,534; Conte *et al.*, U.S. Patent No. 6,294,200).

2. In preparing formulations of the invention, a wet granulate is formed from indapamide, lactose monohydrate, and a binder. The dried granulate is then homogenized with hypromellose and lubricants to provide the sustained release formulation as defined, e.g., by claim 1. Because of the high percentage of hypromellose in the formulation, the particle size of the granulate affects the homogeneity of the indapamide in the formulation and therefore the control of indapamide release. Hypromellose used in pharmaceutical formulations has a relatively small particle size and will provide the most homogenous formulation when the granulate of active ingredient is of similar size. Surprisingly, it has been found that copovidone,

but not povidone, provides a granulate with a superior particle size distribution for use in the present formulation. This may be shown by a particle size analysis.

3. I carried out or caused to be carried out the following analyses comparing granulate size between a granulate of the invention based on copovidone and an identical granulate with povidone.

4. In one batch of granulate, 25.4 g of indapamide and 224.6 g of lactose monohydrate was mixed manually, the mixture poured into a granulate-mixer together with 507.0 g of lactose monohydrate, and mixed about 1 minute with the main agitator speed at 200 rpm. An additional 507.0 g of lactose monohydrate and 60.0 g copovidone were added and all the components mixed for 1 minute with the main agitator speed at 200 rpm and the side agitator speed at 400 rpm. To this mixture, 100.0 g of purified water was added and mixed about 1 minute with the main agitator speed at 200 rpm and the side agitator speed at 400 rpm. The granulation process was then performed by agitating the mixture an additional 3 minutes with the main agitator speed at 400 rpm and the side agitator speed at 400 rpm. The wet granulate was rubbed through a screen with 2.5 mm mesh and dried in a fluidal drier at a temperature of 40 °C to a humidity content of below 1%. The dried granulate was sieved through a screen with 1.2 mm mesh.

5. The process described in paragraph 3 was repeated using 60.0 g of povidone in place of copovidone to produce a second batch of granulate.

6. Each batch was fed into a column with sieves of different sizes arranged one below the other from largest (top) to smallest (bottom). Granules too large to pass through the mesh of a particular screen were retained and measured. The amount of residue of granules retained by each screen was measured as a percentage of the total mass of the batch separated on the column of sieves. The total amount of residue retained on the column add up to about 100%. The Table in the Exhibit A shows the results of this experiment.

7. As can be seen from the Table, at a sieve mesh size of 0.4 mm, 58.45% of povidone comprising granulate are held back (see residues on sieve) and only 16.65% pass. In contrast, at the same sieve mesh size, only 16.75% of the copovidone comprising granulate is held back and as much as 65.60% pass through. Only at the mesh sizes of 0.315 mm is the greatest amount of copovidone comprising granulate held back (35.20%), and nearly as much

(28.75%) is held back at the even smaller mesh size of 0.200 mm. This shows that the formulation batch comprising copovidone surprisingly has a smaller granulate size than the batch comprising povidone.

8. The smaller sizes of the copovidone comprising granulate allows for improved homogenization with hypromellose and therefore improved control over the sustained release of the indapamide from the formulation. None of the cited references disclose the claimed formulation or suggest the unexpected results obtained with crospovidone and described in paragraph 7 above.

9. I hereby acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and may jeopardize the validity of the above-referenced application or any patent issuing thereon. All statements made of each declarant's own knowledge are true and all statements made on information and belief are believed to be true.

Katarzyna Jureczek

November 6, 2008
Date

EXHIBIT A

TABLE

Sieve mesh sizes (mm)	Granulate with Povidone		Granulate with Copovidone	
	Residue on sieve (%)	Pass thorough the sieve (%)	Residue on sieve (%)	Pass thorough the sieve (%)
1.250	0.05	99.95	0.10	99.90
1.000	2.15	97.80	2.40	97.50
0.800	3.35	94.45	3.30	94.20
0.630	4.10	90.35	3.35	90.85
0.500	**15.25**	**75.10**	**8.50**	**82.35**
0.400	**58.45**	**16.65**	**16.75**	**65.60**
0.315	**12.20**	**4.45**	**35.20**	**30.40**
0.200	**4.20**	**0.25**	**28.75**	**1.65**
0.125	0.30	0	1.40	0.25
0.100	-	-	0.15	0.10
0.050	-	-	0.10	-